b) assessing the level of an isoprostane molecular marker for lipid peroxidation present in said first sample, wherein said isoprostane molecular marker is selected from the group consisting of $iPF_{2\alpha}$-III, $iPF_{2\alpha}$-VI, and 8,12-*iso*-$iPF_{2\alpha}$-VI; and

c) comparing the level of said isoprostane molecular marker present in said first sample with the level of said isoprostane molecular marker present in a second sample of a tissue or body fluid obtained from an otherwise identical mammal which is not afflicted with an oxidant stress syndrome or disease, wherein an elevated level of said isoprostane molecular marker in said first sample relative to the level of said isoprostane molecular marker in said second sample, is indicative of an elevated level of lipid peroxidation in said mammal, thereby indicating the presence of an oxidant stress syndrome or disease in said mammal.

REMARKS

Claims 1-5 and 8-34 are pending in the application. The present invention relates to methods of measuring the level of lipid peroxidation in a mammal suspected of having Alzheimer's Disease (claims 1-5 and 8-10), methods to diagnose oxidant stress syndrome (Alzheimer's Disease) in a mammal (claims 11-12), methods of measuring the level of an isoprostane marker for lipid peroxidation in a mammal (claims 13-19), methods of identifying a compound useful for treatment of Alzheimer's Disease (claims 20-23), methods of determining the optimal concentration and dosage frequency of such a compound (claims 24-28), methods of identifying a compounds useful for reducing the level of an isoprostane molecular marker for lipid peroxidation (claims 29-32) and kits for diagnosing Alzheimer's Disease in a mammal or for measuring the level of an isoprostane molecular marker for lipid peroxidation in a mammal (claims 33 and 34).

Claim 1 has been amended to correct an typographic error in the amendment of claim 1 in the Response filed on July 17, 2002. Support for this amendment is found in the specification on page 4, line 13, and claim 7 as filed. This amendment introduces no new matter.

Preliminarily, in a Office Action dated February 28, 2002 (Paper No. 4), the Examiner requested an Information Disclosure Statement of "all of the authors works." To comply with this request, Applicants have enclosed herewith a Supplemental Information Disclosure Statement and accompanying 1449 form citing all of the references cited in the specification including the work of the inventors.

Applicants are pleased to acknowledge the withdrawal of the previous rejection of claims 1-23 over Pratico, claims 1-5 and 10-12 over each of Morrow, Roberts, Mardini, Rokach, Pratico, Fitzgerald, Maxey and Reilly, and claims 24-34 over Pratico in the Office Action dated February 29, 2002 (Paper No. 4). There remains a single rejection of the pending claims for lack of enablement under 35 U.S.C. §112, first paragraph. This rejection is raised against claims 24-34 in page 7 in the first Office Action dated February 29 2002 (Paper No. 4). Here, the Examiner raises the same rejection against all of the claims pending in the application, i.e. claims 1-5 and 8-34.

Rejection of claims 1-5 and 8-34 pursuant to 35 U.S.C. § 112, first paragraph

Claims 1-5 and 8-34 stand rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. In the Examiner's opinion, the specification does not provide a written description of any compounds found for effectively for treating Alzheimer's Disease and no other treatments for isoprostane elevating disorders are shown.. Further, the Examiner states that no kits are seen. The Examiner contends that the claims are not taught by the specification as originally filed and much more than routine experimentation would be required to make and use the invention. In the Examiner's view, while screening for drugs is not new, but how to screen for drugs that are useful for treatment of Alzheimer's Disease is not routine.

Applicants respectfully traverse the rejection of claims 1-5 and 8-34, under 35 U.S.C. § 112, first paragraph, for the reasons set forth below.

Applicants' invention includes the identification of a relationship between the level of lipid peroxidation (as measured by the level of isoprostane markers) and an oxidative stress syndrome such as Alzheimer's Disease. It is Applicant's contention, fully supported by the specification, that this connection is described and enabled in the specification, and

therefore the specification and claims meet all of the requirements of 35 U.S.C. § 112, first paragraph.

As an initial matter, it is well-settled that an applicant need not have actually reduced the invention to practice prior to filing in order to satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph. MPEP §2164.02 (citing *Gould v. Quigg*, 882 F.2d 1074 (Fed. Cir. 1987)). Indeed, the invention need not contain a single example if the invention is otherwise disclosed in such a manner that one of skill in the art will be able to practice it without undue experimentation (*In re Borkowski*, 422 F.2d at 908), and "representative samples are not required be the statute and are not an end in themselves" (*In re Robbins*, 429 F.2d 452, 456-457, 166 USPQ 522, 555 (CCPA 1970)). Thus, 35 U.S.C § 112, first paragraph, enablement does not require any working examples.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. MPEP §2164.01 (citing *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976)). The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. *Id.* Further, the specification need not disclose what is well-known to those skilled in the art and preferable omits that which is well-known to those skilled in the art and is already available to the public. MPEP §2164.05(a) (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)). Therefore, under current law, enablement does not require a working example and experimentation is allowed, as long is it is not undue.

In the landmark enablement case of in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), the court discussed the adequacy of disclosure with regard to a patent disclosing an immunoassay method for the detection of hepatitis B antigen using monoclonal antibodies. The *Wands* Court noted that of 143 hybridomas produced, only nine were assayed and, of those, only four hybridomas secreted IgM antibodies and exhibited a binding affinity constant for the HBsAg determinants of at least 10^9 M^{-1}, a "respectable 44 percent rate of success." *In re Wands*, 8 USPQ2d at 1406. Finding the claims were enabled, the *Wands* Court stated:

> Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known.

> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. No evidence was presented by either party on how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen.

In re Wands, 8 USPQ2d at 1406 (emphasis added). Therefore, where, as disclosed in the present specification, the art typically measures markers in tissues and body fluids, screens compounds for biological activity and/or properties, where compounds and their uses and markers for measuring the activity of the compounds are disclosed in the specification as filed, where the specification discloses specific compounds and specific markers, demonstrating extensive reduction to practice, one skilled in the art would not require undue experimentation to identify the compounds having the desired biological function of being candidate compounds for treatment of Alzheimer's disease.

Thus, where one skilled in the art routinely measures markers in tissues and body fluids and screens compounds for treating diseases, and where compounds for treating diseases have been reduced to practice, having to do so is not the undue experimentation proscribed by 35 U.S.C. § 112, first paragraph, under the reasoning of *In re Wands*.

In *In re Angstadt*, 190 USPQ 214 (CCPA 1976), the court addressed the level of experimentation in an unpredictable art, *i.e.*, the chemical arts, where the claimed invention involved a method of catalytically producing hydroperoxides where the specification admitted that not all disclosed complexes produced the hydroperoxides. The *Angstadt* Court, holding that the invention as claimed was enabled, reasoned:

> We note that many chemical processes, and catalytic processes particularly, are unpredictable. . . .
>
> Appellants have apparently not disclosed every catalyst which will work; they have apparently not disclosed every catalyst which will not work. The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with every species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with "thousands" of examples or the disclosure of "thousands" of catalysts along with information as to whether each exhibits catalytic behavior resulting in the

> production of hydroperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid "literal" infringement of such claims by merely finding another analogous catalyst complex which could be used in "forming hydroperoxides."
>
> *In re Angstadt*, 190 USPQ at 218 (citations omitted).

Thus, where methods for assessing whether a claimed method of identifying a compound capable of treating Alzheimer's disease having the utility of the claimed methods is enabled, and compounds are well-known in the art and/or disclosed in the specification, and where working examples are disclosed (see Figures 1-7 and Examples 1 and 2), it would not be undue experimentation to screen and identify compounds which have the disclosed utility where the art typically engages in such experimentation.

More recently, in *Ex parte Mark*, 12 USPQ2d 1904 (Bd. Pat. App. & Int. 1989), the Board reversed the Examiner's rejection for lack of enablement under 35 U.S.C. § 112, first paragraph, with regard to an application involving admittedly "innumerable" muteins comprising a non-essential cysteine which exhibit biological activity after modification to substitute the cysteine. In reversing the Examiner, the *Mark* Court stated:

> To the extent that the examiner is concerned that undue experimentation would be required to determine other proteins suitable for use in the present invention, we find [an applicant]'s declaration to be persuasive that only routine experimentation would be needed for one skilled in the art to practice the claimed invention for a given protein. The fact that a given protein may not be amenable for use in the present invention in that the cysteine residues are needed for the biological activity of the protein does not militate against a conclusion of enablement. One skilled in the art is clearly enabled to perform such work as needed to determine whether the cysteine residues of a given protein are needed for retention of biological activity.

Ex parte Mark, 12 USPQ2d at 1907. Therefore, where one skilled in the art routinely assays the compounds (*e.g.*, compounds capable of lowering isoprostane levels) for the asserted utility (*e.g.*, treating a disease), it is not undue experimentation for them to do so.
In view of the recited legal standard, under the present patent law, claims 1-5 and 8-34 are amply enabled by the specification as filed under 35 U.S.C. §112, first paragraph. The specification amply supports these claims because the skilled artisan, armed with the methods and the markers disclosed in the specification, would have been able to measure lipid peroxidation in a mammal, diagnose Alzheimer's disease in a mammal, measure the level of an isoprostane molecular marker in a mammal, identify a compound useful for reducing the level of an isoprostane marker for lipid peroxidation molecular marker for lipid peroxidation in the tissue of a mammal, identify an effective amount, optimal concentration, or optimal dosage frequency of a compound useful for the treatment of Alzheimer's disease in a mammal, and make kits for measuring isoprostane markers in tissue and bodily fluids and for diagnosing Alzheimer's disease as recited in the claims, and to practice the invention commensurate with the scope of the claims without undue experimentation.

The specification fully supports the invention of claims 1-5 and 8-10, which pertains to a method for measuring the level of lipid peroxidation in a mammal suspected of having Alzheimer's disease. The alleged absence of disclosure of specific compounds and methods useful for treating Alzheimer's diseases has no bearing on the enablement of the invention of these claims because this invention pertains to measuring lipid peroxidation, not treating Alzheimer's disease. Further, the alleged absence of disclosure of kits is equally irrelevant because no kits are recited in these claims. The specification fully supports the enablement of these claims. Example 2 is a working example wherein the method of the invention was used to measure the levels of isoprostane markers in the cerebrospinal fluid, urine and plasma of patients suspected of having Alzheimer's disease. Further, it is well-known in the art that isoprostanes are molecular markers of lipid peroxidation both *in vitro* and *in vivo* (see, for example, Patrona and Fitzgerald, 1997, Arterioscl. Thromb. Biol. 17:2309-2315). Therefore, specification fully supports the use of the method of measuring

lipid peroxidation in a mammal suspected of having Alzheimer's disease without undue experimentation.

The specification fully supports the invention of clams 11-12, which pertains to a method of diagnosing Alzheimer's disease in a mammal. The alleged absence of disclosure of specific compounds and methods useful for treating Alzheimer's diseases has no bearing on the enablement of these claims because the invention pertains to diagnosing Alzheimer's disease, not treating Alzheimer's disease. Further, the alleged absence of disclose of kits is equally irrelevant because no kits are recited in these claims. The specification fully supports the enablement of these claims. Example 2 is a working example wherein the method of the invention was used to measure the levels of isoprostane markers in the cerebrospinal fluid, urine and plasma of patients suspected of having Alzheimer's disease. The level of an isoprostane marker is shown to be significantly higher in a patient suspected of having Alzheimer's disease than in a patient not suspected of having Alzheimer's disease. Example 2 is therefore a working example which discloses the use of the method of claims 11-12 to diagnose Alzheimer's disease in a mammal. The specification further discloses this diagnosis method by indicating the range of isoprostane marker level in a bodily tissue or fluid that would indicate a diagnosis of an oxidative stress syndrome or disease, such as Alzheimer's disease (Specification, page 18, lines 9-22). Therefore, specification fully supports the method of diagnosing Alzheimer's disease in a mammal without undue experimentation.

The specification fully supports the invention of claims 13-19, which pertains to a method for measuring the level of an isoprostane marker in a mammal using a step utilizing a total lipids extraction method. The alleged absence of disclosure of specific compounds and methods useful for treating Alzheimer's diseases has no bearing on the enablement of the invention of these claims because the invention pertains to measuring an isoprostane marker, not treating Alzheimer's disease. Further, the alleged absence of disclosure of kits is equally irrelevant because no kits are recited in these claims. The specification fully supports the enablement of these claims. Example 1 is a working example wherein total lipids were extracted from tissue to isolate and effectively measure isoprostane molecular markers in brain tissue (specification, page 29, lines 5-12). The specification

further discloses how the total lipid extraction method can be adapted to measure isoprostane molecular markers in bodily fluids (specification, page 18, line 31 through page 19, line 5). Therefore, specification fully supports the use of the method for measuring the level of an isoprostane marker in a mammal using a step utilizing a total lipids extraction method without undue experimentation.

The specification fully supports the invention of claims 29-32, which pertains to a method for identifying a compound useful for reducing the level of an isoprostane molecular marker for lipid peroxidation in the tissue of a mammal, and the invention of claims 20-23, which pertains to a method for identifying a compound useful for the treatment of Alzheimer's disease in a mammal. The Examiner concedes that one routinely screens compounds for treating diseases (Office Action dated Sept. 24, 2002, page 3). However, the Examiner reasons that while screening drugs in not new, how to screen effectively and successfully find an effective treatment for Alzheimer's disease is not routine. The "treatment of Alzheimer's disease" is defined in the specification to include "alleviating one or more of its symptoms" (specification, page 12, line 24). The specification discloses that one of the symptoms of Alzheimer's disease is an increase in isoprostane molecular markers in the tissues and body fluids of Alzheimer's patients (specification, page 30, paragraph 1, and page 36, line 30 to page 37, line 1). Therefore, a compound useful for treating Alzheimer's disease is one that reduces the level of an isoprostane molecular marker in the tissues and body fluids of a patient. The specification fully supports the enablement of these claims. Example 1 is a working example wherein total lipids were extracted from tissue to isolate and effectively measure isoprostane molecular markers in brain tissue (specification, page 29, lines 5-12). Example 2 is a working example wherein the levels of isoprostane markers were measured in the cerebrospinal fluid, urine and plasma of patients suspected of having Alzheimer's disease. The specification further discloses specific compounds that inhibit lipid peroxidation *in vivo*, i.e. vitamin E, vitamin C, ibuprofen and aspirin, and suggested dosage levels (see specification, page 19, line 20 to page 20, line 8) that one of skill in the art could use as guidance of specific compounds and treatment methods to use with the screening method of claims 29-32. Further, compounds similar in structure and/or biological effect and their methods of their use are well known in the art. One of skill in the art would therefore be

able to determine the dosages and treatment methods for similar compounds without undue experimentation (see, MPEP § 2164.01(c)). One of skill in the art could easily combine the methods to measure the levels of isoprostane molecular markers in tissues and body fluids of a mammal described in the working examples with what is well-known in the art and disclosed in the specification regarding specific compounds and treatment methods to successfully practice without undue experimentation the method of claims 29-32 for identifying a compound useful for reducing the level of an isoprostane molecular marker for lipid peroxidation in the tissue of a mammal.

The specification fully supports the invention of claims 24-28, which pertain to methods for identifying an effective amount, optimal concentration, or optimal dosage frequency of a compound useful for a treatment of Alzheimer's disease in a mammal. The alleged lack of description of kits in the specification does not render these claims non-enabled because kits are not recited in these claims. Example 2 is a working example wherein the levels of isoprostane markers were measured in the cerebrospinal fluid, urine and plasma of patients suspected of having Alzheimer's disease, and the level of an isoprostane marker is shown to be significantly higher in a patient suspected of having Alzheimer's disease than in a patient not suspected of having Alzheimer's disease. These data establish the connection between Alzheimer's disease and elevated levels of isoprostane molecular markers in the body fluids and tissues. Therefore, the specification fully supports the use of the methods for identifying the effective amount, optimal concentration, or optimal dosage frequency of a compound useful for the treatment of Alzheimer's disease in a mammal without undue experimentation.

The specification fully supports the invention of claims 33 and 34, which pertain to kits for measuring isoprostane molecular markers in tissue and body fluids, and for diagnosing Alzheimer's disease. The alleged absence of disclosure of specific compounds and methods useful for treating Alzheimer's disease has no bearing on the enablement of these claims because the invention pertains to measuring isoprostane molecular markers and diagnosing Alzheimer's disease, not treating Alzheimer's disease. The Examiner alleges that no kits are seen in the specification, however this is not the case. The components of the kits are disclosed in the specification (pages 25-27), and are recited in claims 33 and 34 as filed.

Further, the Examples 1 and 2 provide the disclosure of how to use the kits to measure isoprostane markers or diagnose Alzheimer's disease. Therefore, specification fully supports making and using the kits for measuring isoprostane molecular markers in tissue and body fluids, and for diagnosing Alzheimer's disease without undue experimentation.

Applicants respectfully submit that claims 1-5 and 8-34 are amply supported by the disclosure provided in the specification as filed, and that numerous working examples, which are not required under the present law for enablement, are provided. Therefore, undue experimentation would not be required for one of skill in the art to make and use the full scope of the invention as recited in claims 1-5 and 8-34. Thus, the Applicants respectfully request that this rejection be reconsidered and withdrawn.

Summary

Applicants respectfully submit that each rejection of the Examiner to the claims of the present application has been overcome or is now inapplicable, and that each of currently pending claims 1-5 and 8-34 is in condition for allowance. Reconsideration and allowance of claims 1-5 and 8-34 are respectfully requested at the earliest possible date.

Respectfully submitted,

FITZGERALD *ET AL.*

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Supplemental IDS, Form 1449 and copies of recited references

Marked Up Copy of the Claims

Claim 1 has been amended as follows:

1. (Twice Amended) A method of measuring the level of lipid peroxidation in a mammal suspected of having an oxidant stress syndrome or disease, wherein said oxidant stress syndrome or disease is Alzheimer's disease, said method comprising

a) obtaining a first sample of a tissue or body fluid from said mammal;

b) assessing the level of an isoprostane molecular marker for lipid peroxidation present in said first sample, wherein said isoprostane molecular marker is selected from the group consisting of $iPF_{2\alpha}$-III, $iPF_{2\alpha}$-VI, and 8,12-*iso*-$iPF_{2\alpha}$-VI; and

c) comparing the level of said isoprostane molecular marker present in said first sample with the level of said isoprostane molecular marker present in a second sample of a tissue or body fluid obtained from an otherwise identical mammal which is not afflicted with an oxidant stress syndrome or disease, wherein an elevated level of said isoprostane molecular marker in said first sample relative to the level of said isoprostane molecular marker in said second sample, is indicative of an elevated level of lipid peroxidation in said mammal, thereby indicating the presence of an oxidant stress syndrome or disease in said mammal.